Comments on S7B

Timing of studies (Section 2.4)

The recommendation for the nonclinical studies to be carried out early is useful.

Nomenclature of K channels

The latest K channel nomenclature for hERG and KvLQT1 channels is KCNH2 and KCNQ1, respectively. Whilst hERG is still the preferred/most widely used name for the former channel, KvLQT1 is now more frequently referred to as KCNQ1 in the literature so the guideline should be updated to use this name.

Use of positive controls and reference compounds (Section 3.1.1)

It is suggested that while positive controls should be used in *in vitro* and *in vivo* studies, they are not necessary in every *in vivo* study. Why is this distinction made?

In vitro electrophysiology studies (Section 3.1.2)

This section mentions measuring APD30 to obtain information on Phase 2 of the action potential and triangulation. In dog PF preparations (and possibly other preparations) this is not the best measure during the plateau; APD40 is more appropriate. The Guideline should be modified to "APD30 or APD40". There is some literature data to support this.

Testing metabolites (Section 3.1.2) (**should this be 3.1.3 line 282?**)

This section could be read as requiring that, in the event of a discrepancy between *in vivo* and *in vitro* data, all metabolites be tested in an *in vitro* system. Assuming this is not what is meant, clarification is needed. Maybe "metabolites" could be changed to "major metabolites".